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#16

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 16

Application Number: 08/289,290
Filing Date: August 11, 1994
Appellants: Ralph H. Weichselbaum, Dennis E. Hallahan, Donald W. Kufe, Vikas P. Sukhatme

Steven L. Highlander
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed December 12, 1997.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

Written Request for Oral Hearing, Fee
DOCKETED
FOR 5-12-98
BY 99

Reply Brief
DOCKETED
FOR 5-12-98
BY 99
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A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is incorrect because claim 22 has not been cancelled. Apparently the confusion on this point (on the part of both the Examiner and Appellants) arose when the cancellation of claims 23-25 was incorrectly entered by the clerk as cancellation of claims 22-24 in the index of claims. This error is not believed to be significant enough to warrant re-opening of prosecution, since all claims are rejected under 112 on the same grounds, and Appellants have traversed all the art rejections on the same grounds. A correct statement of the status of the claims (after entry of the amendment after final) is as follows:

Claims 1-3, 6, 8-14, 17-22 and 26-36 are on appeal.

(4) Status of Amendments After Final

The amendment after final rejection filed on December 12, 1997 has been entered.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is essentially correct. After entry of the amendment after final rejection, the remaining issues are:

1. Is the specification enabling for the full scope of claims 1, 3, 6, 8-14, and 17-22, 26-30 and 35?

2. Are claims 1-3, 6, 8-14, 17-22 and 26-36 obvious over the prior art?

(7) Grouping of Claims

Appellant's brief includes a statement that the claims do not stand or fall together and provides reasons in the argument (with regard to the rejections under § 112) as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

A substantially correct copy of appealed claims 1-3, 6, 8-14, 17-22 and 26-36 appears on pages 1-3 of the Appendix to the appellant's brief. The minor errors are as follows: Claim 17 has not been cancelled (cancellation was not requested in the amendment after final rejection).

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

5,264,618 FELGNER et al. 11-93

Vile, R.G. et al. "*In Vitro* and *In Vivo* Targeting of Gene Expression in Melanoma Cells." Cancer Research, vol. 53 (March 1, 1993), pp. 962-967.

Breakefield, X.O. et al. "Herpes Simplex Virus For Gene Delivery To Neurons." The New Biologist, vol. 3, no. 3 (March, 1991), pp. 203-218.

Arai, K. et al. "Cytokines: Coordinators of Immune and Inflammatory Responses." Annual Review of Biochemistry, vol. 59 (1990), pp. 783-785.

Mattern, J. et al. "Human tumor xenografts as model for drug testing." Cancer and Metastasis Reviews, vol. 7 (1988), pp. 263-284.

Hallahan, D.E. et al. "The Interaction Between Recombinant Human Tumor Necrosis Factor and Radiation In 13 Human Tumor Cell Lines." International Journal of Radiation Oncology Biology Physics, vol. 19 (1990), pp. 69-74.

Hallahan, D.E. et al. "Phase I Dose Escalation Study Of Tumor Necrosis Factor And Radiation." International Journal of Radiation Oncology Biology Physics, vol. 27, supplement 1 (1993), p. 184.

Teng, M.N. et al. "Long-term inhibition of tumor growth by tumor necrosis factor in the absence of cachexia or T-cell immunity." Proceedings of the National Academy of Sciences, USA, vol. 88 (May, 1991) pp. 3535-3539.

Neta, R. et al. "Radioprotection with Cytokines - Learning from Nature to Cope with Radiation Damage." Cancer Cells, vol. 3, no. 10 (October 1991), pp. 391-396.

Herz, J. et al. "Adenovirus-mediated transfer of low density lipoprotein receptor gene acutely accelerates cholesterol clearance in normal mice." Proceedings of the National Academy of Sciences, USA, vol. 90 (April 1993), pp. 2812-2816.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

REJECTION UNDER § 112, FIRST PARAGRAPH

Claims 1, 3, 6, 8-14, 17-22, 26-30 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods utilizing the tumor necrosis factor (TNF)-encoding gene, does not reasonably provide enablement for methods utilizing genes encoding any and all radiosensitizing and radioprotecting polypeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not adequately teach how to use *in vivo* methods requiring expression of genes other than the tumor necrosis factor α (TNF) gene, or pharmaceutical compositions comprising other genes. Most cytokines have pleiotropic effects; they interact with each other and with various biochemical pathways (Arai et al., p. 785). One skilled in the art can not predict the outcome of expressing any and all cytokines in a mammal, because the intact animal is much more complicated than *in vitro* systems. The specification does not adequately teach which cytokines will have protective effects or which will have sensitizing effects. The systemic effects of expressing any cytokine are unpredictable, particularly if expression is not confined to any particular location.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to make and use the full scope of the claimed invention. This is particularly true

given the breadth of the claims, the amount of experimentation necessary, the nature of the invention, the state of the prior art, the scarcity of guidance regarding non-exemplified embodiments, and the unpredictable nature of the art.

REJECTIONS UNDER § 103(a)

Claims 1-3, 6, 17, 18, 29, 31, 33, 35 and 36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan et al. (1990) in view of Teng et al., Neta et al. and Vile et al. Hallahan et al. show that TNF and ionizing radiation act synergistically to kill human tumor cells *in vitro* (entire document). Hallahan et al. report that cell killing is maximized by addition of TNF 4-12 hr prior to irradiation, i.e. the TNF sensitizes tumor cells to the effects of radiation (p. 73, col. 2). Hallahan et al. disclose that TNF enhances the effect of radiation in mice *in vivo*, and suggest clinical use of TNF in combination with radiation (p. 74). Hallahan et al. do not disclose methods in which a TNF gene is transfected into cells to sensitize or protect tumorous and normal cells, respectively, prior to irradiation. Teng et al. disclose experiments in which murine tumor cells were transfected with the human TNF gene under control of the CMV intermediate early promoter, then implanted into nude mice (entire document). Teng et al. show that transfected tumor cell lines which produce moderate levels of TNF grow more slowly than non-transfected cell lines when implanted, and that this level of TNF production does not cause serious weight loss (e.g. Table 1). Neta et al. teach that TNF can simultaneously radiosensitize tumor cells and radioprotect normal cells (pp. 391-392; p. 394, col. 2). Other cytokines such as IL-1 are reported to have similar effects. Vile et al.

teach a method for transfecting tumor cells and surrounding normal cells *in vivo* by direct injection of DNA into a tumor (pp. 965-966).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the tumor cell killing method of Hallahan et al. by transfecting tumor cells with the TNF gene as taught by Teng et al. rather than administering TNF directly. One of ordinary skill in the art would have expected that normal cells would be radioprotected by this method, given the teachings of Neta et al. and the knowledge that the DNA injection method of Vile et al. would transfect adjacent normal cells as well as tumor cells. There would have been a reasonable expectation of success, given the finding that TNF produced by a transfected tumor can suppress tumor growth without causing severe systemic side effects, as taught by Teng et al. One of ordinary skill in the art would have been motivated by the explicit suggestion of Hallahan et al. to use the combination of radiation and TNF *in vivo*, and by the readily apparent advantage of supplying TNF locally without causing cachexia as taught by Teng et al. Furthermore, claims 18 (and subsequent dependent claims) and 36 encompass transfection of cultured cells. There was an even greater expectation that transfected, cultured cells expressing TNF would be successfully radiosensitized or radioprotected (depending on the type of cell), given the *in vitro* data of Hallahan et al. With regard to claim 31 (and subsequent dependent claims), the claim requires only that the TNF be expressed, not that any therapeutic benefit be obtained. There was at least a reasonable expectation that TNF would be expressed *in vivo* by transfecting cells with the gene construct of Teng et al. Thus, the

invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 9, 19 and 20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. as applied to claims 1-3, 6, 17, 18, 29, 31, 33, 35 and 36 above, and further in view of Felgner et al. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. do not teach a method wherein the DNA construct is administered in liposomes. Felgner et al. teach liposome compositions for administering DNA to animals *in vivo* (e.g. col. 8). Felgner et al. teach that the disclosed lipids provide more effective intracellular delivery (col. 8, line 66-68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. by injecting the DNA in a liposome preparation as taught by Felgner et al. One of ordinary skill in the art would have been expected this modification to increase the efficiency of DNA delivery as taught by Felgner et al. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 10, 12-14, 19, 21, 26-28, 30 and 32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. as applied to claims 1-3, 6, 17, 18, 29, 31, 33, 35 and 36 above, and further in view of Herz et

al. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. do not teach a method wherein the DNA construct is administered as an adenoviral vector. Herz et al. show that an adenoviral vector can be used to transiently express heterologous DNA under control of the CMV promoter in mice (entire document). Herz et al. show that intravenous administration of the virus results in transfection of hepatic parenchymal cells (p. 2815).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. by administering the TNF gene in an adenoviral vector as taught by Herz et al. One of ordinary skill in the art would have been motivated to do so in order to target liver parenchymal cells, for example. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 11, 19, 22, 30 and 32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. as applied to claims 1-3, 6, 17, 18, 29, 31, 33, 35 and 36 above, and further in view of Breakefield et al. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. do not teach a method wherein the

DNA construct is administered as a HSV vector. Breakefield et al. teach that HSV vectors can be used to express heterologous DNA in neurons (pp. 211-213).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. by administering the TNF gene in a HSV vector as taught by Breakefield et al. One of ordinary skill in the art would have been motivated to do so in order to transfect neuronal cells. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 34 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. as applied to claims 1-3, 6, 17, 18, 29, 31, 33, 35 and 36 above, and further in view of Mattern et al. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. do not teach a method wherein the DNA construct is administered to a human subject. Mattern et al. teach that human tumor xenografts are an art-accepted model for human cancer (entire document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to extend the methods of Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. to human patients. There would have been a reasonable expectation of success, given the fact that TNF and radiation were known to have a synergistic effect on human tumor cells

as taught by Hallahan et al., and given the knowledge that the nude mouse model of Teng et al. was expected to reasonably model human cancer as taught by Mattern et al. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-3, 6, 17, 18, 29, 31 and 33-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan (1993) in view of Teng et al. and Vile et al. Hallahan et al. disclose phase I clinical trials in which TNF was administered to patients prior to radiation treatment (entire document). Hallahan et al. teach that enhancement of tumor control and radioprotection have been demonstrated *in vivo* when TNF is administered prior to irradiation. Hallahan et al. specifically suggest trials of "TNF gene therapy localized to tumors in combination with radiation." Hallahan et al. do not teach materials and methods for "TNF gene therapy." Teng et al. disclose experiments in which murine tumor cells were transfected with the human TNF gene under control of the CMV intermediate early promoter, then implanted into nude mice (entire document). Teng et al. show that transfected tumor cell lines which produce moderate levels of TNF grow more slowly than non-transfected cell lines when implanted, and that this level of TNF production does not cause serious weight loss (e.g. Table 1). Vile et al. teach a method for transfecting tumor cells and surrounding normal cells *in vivo* by direct injection of DNA into a tumor (pp. 965-966).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to transfect tumor cells with a gene encoding TNF prior to radiation therapy, as

suggested by Hallahan et al. It would have been obvious to use the CMV/TNF construct of Teng et al., transfecting by direct injection as taught by Vile et al. There would have been a reasonable expectation of success, given the known radiosensitizing and radioprotecting effects of TNF as taught by Hallahan et al., the demonstrated efficacy of the construct of Teng et al., and the expectation that both tumor and normal cells would be transfected by injection as taught by Vile et al. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 9, 19 and 20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan et al. in view of Teng et al. and Vile et al. as applied to claims 1-3, 6, 17, 18, 29, 31 and 33-35 above, and further in view of Felgner et al. Hallahan et al. in view of Teng et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al. and Vile et al. do not teach a method wherein the DNA construct is administered in liposomes. Felgner et al. teach liposome compositions for administering DNA to animals *in vivo* (e.g. col. 8). Felgner et al. teach that the disclosed lipids provide more effective intracellular delivery (col. 8, line 66-68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view of Teng et al. and Vile et al. by injecting the DNA in a liposome preparation as taught by Felgner et al. One of ordinary skill in the art would have been expected this modification to increase the efficiency of DNA

delivery as taught by Felgner et al. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 10, 12-14, 19, 21, 26-28, 30 and 32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan et al. in view of Teng et al. and Vile et al. as applied to claims 1-3, 6, 17, 18, 29, 31 and 33-35 above, and further in view of Herz et al. Hallahan et al. in view of Teng et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al. and Vile et al. do not teach a method wherein the DNA construct is administered as an adenoviral vector. Herz et al. show that an adenoviral vector can be used to transiently express heterologous DNA under control of the CMV promoter in mice (entire document). Herz et al. show that intravenous administration of the virus results in transfection of hepatic parenchymal cells (p. 2815).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view of Teng et al. and Vile et al. by administering the TNF gene in an adenoviral vector as taught by Herz et al. One of ordinary skill in the art would have been motivated to do so in order to target liver parenchymal cells, for example. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 11, 19, 22, 30 and 32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hallahan et al. in view of Teng et al. and Vile et al. as applied to claims 1-

3, 6, 17, 18, 29, 31 and 33-35 above, and further in view of Breakefield et al. Hallahan et al. in view of Teng et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al. and Vile et al. do not teach a method wherein the DNA construct is administered as a HSV vector. Breakefield et al. teach that HSV vectors can be used to express heterologous DNA in neurons (pp. 211-213).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view of Teng et al. and Vile et al. by administering the TNF gene in a HSV vector as taught by Breakefield et al. One of ordinary skill in the art would have been motivated to do so in order to transfect neuronal cells. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

(11) Response to Argument

REJECTION UNDER § 112, FIRST PARAGRAPH

Appellants argue that the Examiner is requiring proof that each claimed polypeptide works as predicted. This is not true; no such requirement was ever made. However, it is well established that, in unpredictable arts, more than one example may be required to enable a broad genus (MPEP 2164.03). Appellants further argue that the claims are limited to situations in which the methods work, and that the specification teaches methods to determine

which polypeptides will work. This may be true, but the actual work of determining which genes will be effective for therapy is still left for others.

Appellants argue that claims reciting TNF should be separately patentable. This rejection has been withdrawn for claim 2, the only claim which is limited to the TNF gene.

Appellants argue that there is no reason why one would not accept *in vitro* results as predictive for *in vivo* gene therapy. This line of argument is contrary to Appellants' arguments regarding the rejections under § 103. The prior art actually provided much more information about TNF than the specification provides about other potentially useful polypeptides, but Appellants apparently feel that the prior art was not enabling for TNF.

Regarding means of delivering the DNA construct, this aspect of the rejection has been withdrawn because the claims now all recite that the gene is delivered to the target cell. Thus the remainder of Appellants' arguments are moot.

REJECTIONS UNDER § 103(a)

Appellants traverse all of the rejections on the same grounds, so they will be treated together.

Appellants argue that providing a polypeptide to a cell is not "reasonably equivalent" to synthesizing the polypeptide within a cell. This argument is not persuasive because it is not supported by any objective evidence.

Appellants argue that the rejections do not meet the standards for obviousness set forth in *In re O' Farrell* and *In re Vaeck*, but do not provide any reasons why they do not.

Appellants argue that these are "obvious to try" rejections, i.e. that there was not a reasonable expectation of success. This argument is not persuasive because Hallahan et al. (1993) specifically suggested doing exactly what Appellants have done, stating, "phase I trials of TNF gene therapy localized to tumors in combination with radiation are warranted." If (presumably) responsible physicians were advocating clinical trials, surely they must have expected that there was at least a reasonable chance that the method would be successful. Thus it was not merely obvious to try, but obvious to do.

Appellants' argument seems to rest on the contention that expressing TNF within a cell (from a transfected gene) is somehow different from providing TNF to the cell from without. This argument is flawed for several reasons.

First, there is no evidence on the record to support the idea that endogenously produced TNF would be expected to have different effects than exogenously supplied TNF. It is well established that attorney's arguments are no substitute for objective evidence (MPEP 2145(a)).

Second, it was known that TNF produced by a transfected cell is secreted from the cell (Teng et al.). Once the TNF is secreted, it becomes "exogenous," and should behave exactly the same as exogenously supplied TNF. Neither the specification nor the claims indicate that the TNF gene should be engineered so that the polypeptide is not secreted, and indeed Example VII shows that transfected cells secrete TNF into the culture medium (p. 45, lines 23-24). The Examiner can not understand why Appellants believe that there is a distinction between cells made according to the claimed method, transfected *in situ* and secreting TNF,

and the cells of Teng et al., transfected *in vitro* and secreting TNF *in vivo* after implantation. Furthermore, it was known that secretion of the TNF was required for its biological activity, since Teng et al. showed that TNF-neutralizing antibodies inhibited the TNF effect. Finally, with regard to claims 12-14, the claims recite that the polypeptide is secreted from the transfected cell.

Third, Vile et al. showed that when a vector was injected directly into a tumor, a maximum of 10-15% of the tumor cells were transfected (sentence bridging pp. 965-966). So even if one accepted Appellants' unsupported argument regarding internally produced TNF, at least 85% of the tumor cells would be non-transfected and would therefore encounter "exogenous" TNF secreted by the smaller fraction of transfected cells.

Appellants argue that Teng et al. does not show that TNF would have an effect on tumor cells in conjunction with radiation. This argument is not persuasive because the combined effect of TNF and radiation was well established by Hallahan et al. (1990 and 1993) and Neta et al. Appellants further argue that it is important that growth of transfected cells which did not secrete TNF was not inhibited *in vivo* (Teng et al.). It is not clear why Appellants consider this important. If Appellants are concluding that this particular cell line produced TNF but did not secrete it, this conclusion is not supported by any evidence in the reference itself (or elsewhere). More likely, the cell line contained plasmid DNA which had somehow been rendered nonfunctional (e.g. by mutation). Teng et al. do not place any

emphasis on this result, and it appears that this particular cell line was simply used as a negative control.

Appellants argue that the specification shows that treated tumors regressed, which would not have been predicted from the prior art. This argument is not persuasive because Hallahan et al. (1993) reported complete tumor regression and also stated, "*in vivo* studies have demonstrated enhancement of tumor control...when TNF is added prior to irradiation." These facts were what led Hallahan et al. to specifically suggest the claimed invention.

Finally, Appellants' arguments do not apply to some of the claims. Claims 12-14, 18-22 and 26-28 all encompass treatment of cultured cells *in vitro*. Appellants have presented no reason why one of ordinary skill in the art would not have had a reasonable expectation of success in using these methods *in vitro*. Similarly, claim 36 is simply a method for *in vitro* testing of polypeptide factors for properties known in the prior art. Claims 29-34 are simply methods of increasing the level of a polypeptide factor (such as TNF) in a mammal by administering a vector encoding the factor, and compositions comprising a vector encoding the factor. Appellants have presented no argument or evidence to suggest that these would not have been obvious.

In the event that it is concluded that the specification does demonstrate unexpected results, it is pointed out that any unexpected results are limited to TNF, and hence not commensurate with the scope of the claims (except claim 2).

Serial Number: 08/289,290

Art Unit: 1632

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

BRC
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